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Neurological Aspects of THC as a Treatment for Generalized Anxiety

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Marijuana/Cannabinoids therapeutic effects on Anxiety

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Abstract

Currently, 1 in 13 people (264 million people) are diagnosed in the world with anxiety disorder. Anxiety is a disorder that causes random or triggered panic attacks due to an imbalance of neurotransmitters in the limbic system of the brain. Marijuana (*Cannabis sativa*) contains high levels of delta-9-tetrahydrocannabinol (THC). THC acts as a neurotransmitter and is able to attach to molecules called cannabinoid receptors on neurons, activate them, which results in changes in mental and physical functions. The neural communication network used by THC neurotransmitters is known as the endocannabinoid system. The endocannabinoid system and the limbic system are interconnected and share the use of cannabinoid receptors. Therefore, THC derived medications has a potential to alleviate anxiety symptoms by rebalancing of neurotransmitters in the limbic system.

Introduction

Marijuana, also known as Cannabis, contains a psychoactive component called delta-9-tetrahydrocannabinol (THC), which essentially causes the “high” effect known from consuming or smoking the plant. Marijuana also contains cannabidiol (CBD) which has shown some medically beneficial effects on serious neurological disorders and more (Zou et al., 2018). *C. sativa* is tall, long, and with narrow leaves, and provides an energizing, stimulating effect, producing a greater amount of THC than CBD. On the other hand, *C. indica* is a short and broad plant with thick, dense leaves, and provides a more relaxing, calming effect, producing an equalized ratio between THC than CBD

(McPartland, 2017). *C. sativa* strain is used in the medical industry because of its ratios between THC and CBD, which is more ideal to reach more audiences including children. The *C. sativa* strains' low CBD and high THC content will cause more of an effect on the CB1 and CB2 production, which comes primarily from the THC component. Marijuana is trending in the medical world, and recently, research has proven that use of cannabinoids might be beneficial on curing and/or alleviating some of the most common diseases/disorders, including anxiety.

Anxiety is a psychiatric disorder that causes panic and apprehension in response to stress. It can be caused by various sources: trauma, genetic inheritance, fear/ phobias, environmental stress, among other things. The disorder effects 18.1% of the U.S. population each year, totaling up to more than 40 million people (ADAA). Anxiety causes chemical changes in the limbic system, which includes the amygdala, hippocampus and the hypothalamus of the brain (Zou et al., 2018).

The endocannabinoid system (ECS) is a multi-region complex of several brain areas: medial prefrontal complex, amygloid complex, hippocampus, and the dorsal periaqueductal gray (Murrough, 2015) and overlaps 2/3 of the limbic regions. Current research on the two agonist cannabinoid receptors, CB1 and CB2, are helping to understand the role of cannabis on anxiety.

In this review, research about the endocannabinoid system, CBR receptors & signaling within the central nervous system, the significance of the overlapping systems between ECS and anxiety, and how cannabinoids & related medicines are being used and examined for anxiety will all be analyzed.

The Endocannabinoid System

Did you know that everyone has an endocannabinoid system? The ECS is self-governed and has receptors all over the body, your body even produces a very small number of natural cannabinoids. However, when a person consumes THC from marijuana in whichever form they prefer, there ends up being excess of cannabinoids in the system, disrupting the balance. Cannabinoids don't only just effect the brain, but other regions of the body where the receptors reside.

The ECS involves two cannabinoid receptor that cells in the body express called CB1 and CB2 (these are agonists), these are found in the immune system and very abundant in the central nervous system. The agonists are what really establish the connection between cannabis and the body, these agonists initiate a response once its combined with a receptor (Zou, 2015). It is possible that anxiety can be alleviated with medical marijuana (*sativa*) use due to how closely related the systems are and the interactions and overlap between them.

Endocannabinoid system overlapping the limbic system of Anxiety

The idea of anxiety is linked with fear, and fear is a result of the body responding to a possibly dangerous stimulus, to lead the organism to promote survival (Ruehle et al., 2011). Therefore, anxiety is natural, although disruptions in the balance of the neurotransmitters can cause neurological dysfunctions which the illness anxiety is. Anxiety is frequent occurrence of one or more stimuli triggering the exhausting

symptoms of anxiety, when it's not of dire need to express these symptoms. Those who suffer from anxiety disorder, have an imbalance in the emotional area of the brain of the limbic system (Martin et al., 2013). The limbic system contains some of the same areas of the brain of the endocannabinoid system, controlling the body's perception of senses, pain, fear, stress, mood and more. The crossover of the two systems in the same brain regions play an important role in how the ECS functions in relation in how cannabinoids can effect anxiety. Those with anxiety disorder will have decreased inhibitory signaling or increased excitatory neurotransmission in the communication between brain cells via gamma-amino-butyric acid (GABA - reducing neuronal activity) or glutamate (increasing neuronal activity). When activated by CB1Rs, GABA will have anxiogenic response, inducing anxiety. On the other hand, glutamate creates an anxiolytic response, reducing anxiety. These two neurotransmitters are known in the ECS for possessing cannabinoid CB1 receptors in the axon terminals, when activated, CB1 can play its role in inhibiting the production of GABA by controlling its release (Laaris et al., 2010), therefore, causing a push against the unbalanced neurotransmitters and reducing anxiety's effects. However, just like everything else, CB1R agonists can have pros and cons; too many of the receptors can cause anxiogenic effects, and not enough agonists can lead to anxiolytic effects (Ruehle et al., 2011). Theses two transmitters do not work together, so to regulate anxiety, the focus point is to regulate the both of them equally so that no anxiogenic response occurs.

Studies was conducted by several research teams to test the conation between cannabinoid receptors and the neurotransmitters, there were three main tests used to analyze the levels of stress the subject mice: light/dark box test, elevated plus-maze,

and Vogel conflict test. After a knockout of CB1R was analyzed, comparing wild type mice to mice with the knock out of CBRs, resulted in an anxiogenic response in the mice with the knock out. Although, the study resulted in a strong decrease or increase of an anxiety response, the absence of the CB1R solely depends on which neurotransmitter is more abundant (Ruehle et al., 2011). This study expresses how cannabinoid receptors are bimodal when expressing anxiety, because of the neurotransmitters they interact with. Even directly injected THC into different areas of the brain result in two different dominances of the neurotransmitters. When injected into the prefrontal cortex, there is a anxiolytic effect, versus when injected in the basal amygdala, theres an anxiogenic response (Ruehle et al., 2011). A possible explanation goes along the lines of expression of a dominant neurotransmitter in various areas of the limbic system this all connect to how anxiety works in the body, these results may vary. Another study conducted by Haller and her team to observe the effects of agonist cannabinoids (WIN-55,212) compared to the cannabinoid antagonist (AM-251) in mice and wistar rats, they believed that the variations of the antagonist-agonist interactions were species related. Which makes sense because some animals can be more fearful (increased anxiety) than other animals. For example, smaller, more preyed on animals vs larger, predatory animal would have different triggers for anxiety. In the study, the team hypothesized that the species' effects from cannabinoids were sensitive on expression of GABA and glutamate on anxiety (Haller et al., 2007). During the control period of the experiment, the researchers regulated the mice and rats in a stable lab conditions, so that they can become used to it, and already they seen environmental factors that could effect the experiment (hierarchy/ social status between the animals),

so they separated every subject to focus solely on the behavior, instead of environmental factors. They studied several series of experiments, comparing and contrasting these effects of higher and lower concentration (0.3 mg/kg and 1 mg/kg) of agonists or (1mg) antagonist, light and dark, isolation and combination, and functionality of the subjects in the plus maze, the results followed: the antagonist had an anxiogenic effect on the mice, closed-arm entries were not effected ($P > 0.2$), and open-arm entries were significantly reduced compared to the control ($P<0.003$ & $P= 0.057$); on the other hand, rats didn't respond to the antagonist as the mice, closed-armed entries weren't significantly different ($P< 0.5$), open-armed entries weren't significantly different ($P<0.7$) (Haller et al., 2007). In the mice specifically, the results show that the WIN-55,212 agonist decreased anxiety, but on the other hand, the same agonist created an increase in anxiety in the rats. The article compares the activation of cannabinoid receptors in several species, and there is a significant different in what species' CBR1/CBR2 will release which neurotransmitter. Fortunately, mice and humans have the same reactions when the cannabinoid receptors 1 and 2 are activated.

Cannabinoid receptors and signaling in the limbic system

The receptors of the endocannabinoid system are very much expressed throughout the central nervous system with or without the assistance of cannabis. The CB1 and CB2 receptors are G-protein-coupled receptors (GCPRs), agonists within the endocannabinoid system that are represented across neurological systems, they function together to degrade metabolism, cellular uptake, and endocannabinoid biosynthesis (Pertwee, 2012). The other endocannabinoids that are produced by the

body, anandamide (AEA) and 2-arachidonoylglycerol (2-AG) help activate the CB1 and CB2 receptors and begin the up-regulation/ down-regulation of the psychoactive neurotransmitter balance in the body (Mouhamed et al., 2018). CB1 differs from CB2 because it is localized at the presynaptic terminals, hence their function to inhibit neurotransmitter release and regulate cytokine release; whilst CB2 receptors concentrate in the immune system (Pertwee, 2005). These synapses occur with the brain region of the limbic system specifically the amygdala, which is why it's an important location for intertwining the two systems. The amygdala controls fear response, expressing as symptoms of anxiety, the synapses here are extremely important to the overall expression of GABA and glutamate to determine what actually triggers symptoms in which part of the amygdala. As previously mentioned, the neurotransmitters GABA and glutamate are expressed to create an influx within the nervous system to directly cause anxiogenic or anxiolytic effects on the body. When CB1 is activated, it usually leads to inhibition of release of GABA, using the agonist (as mentioned previously) WIN-55,212 (Ruehle, et al., 2012), this method can be very efficient in the control of anxiogenic effects. However, THC can manifest both anxiolytic and anxiogenic characteristics because when its bound to CB1 receptors, release of both GABA and glutamate compounds (Pertwee, 2005), so it is definitely possible for marijuana to cause anxiety or increase its symptoms. Although, if properly regulated by dosage, and even singling out THC components, it is possible to correct the imbalance and focus on releasing only GABA or only glutamate to properly treat one with anxiety, but only if its known which neurotransmitter is causing the imbalance. The process of

targeting requires more research for progress on using THC neurological aspect for treatment of anxiety.

Drugs targeting cannabinoid receptors to treat anxiety

As the states of the United States are slowly legalizing the use of medicinal marijuana, the government has set very strict guidelines and requirements in the lengthy process from the specific bud to the patient. The most complicated part is educating the physicians on proper criteria on how to prescribe the doses. It is recommended to start low to determine the level of euphoria that the patient experiences to figure out the amount that is best for the patient to acquire and to avoid too high of a dose that can impair cognition of the patient (Murrough et al., 2015). Calcium is a key factor in the middle of the these processes, when AEA, 2-AG, or THC bind with CB1 in the presynaptic terminal, it regulates the amount of calcium then decreases the release of neurotransmitters to travel to the post synaptic terminal. Interferences in this process can lead to many different types of reactions in the body, which is not ideal, therefore controlling this regulation is what the drugs are needed to do. As we know, psychological disorders are usually caused by disfunction or certain imbalances in the neurotransmitters produced in the brain, here is when the endocannabinoid system can come into play. The relation between two systems have been thoroughly researched, and in some cases, there will be up regulation in the endocannabinoid system that causes symptoms of a disorder/disease in which antagonists can aid in down regulation in the neurological balance (Pertwee, 2005), essentially rebalancing the transmitters and stopping symptoms. Pharmacologists will

have to identify specific receptors involved and location of the imbalances to then know what drug and its abundance can solve the issue. In the case of anxiety, drugs already established target serotonin and GABA in the body to regulate symptoms such as: headache pains, insomnia, diarrhea/nausea, appetite decrease, fatigue and cognition issues (Mouhamed et al., 2018). Big “pharma” has worked on synthesizing the creating a version of THC that can be easily administered and can avoid the other effects of marijuana without actually using marijuana, hence there were be neurological effects without the side effects. One of the top choice of treatments for anxiety already in place are benzodiazepines, which enhance the effects of GABA, leading to calming the excited signaling of the neuronal synapses overall (slowing down the release of more neurotransmitters) (Griffin, et al., 2013), which can be used synergistically with other possible treatments for a strong effect on rebalancing the neurotransmitters.

Conclusion

In conclusion, GABA and glutamate are the key components to bridging the gap between the endocannabinoid system and the limbic system. The secret to balancing the neurotransmitters caused by anxiety lies within the mystery of how the receptors release neurotransmitters, which ones and how much. Once that has been discovered, scientists can pin point the stimulating factor from marijuana in the THC molecules to regulate the imbalance and virtually solving the chemical issue with anxiety patient. Therefore, marijuana derived treatments *can* help alleviate symptoms of anxiety, although there is much more research needed to done to achieve that goal. There are many people in the world suffering from anxiety, and the numbers are increasing.

Something needs to be done to lower the stats on this disorder, because it has potential to lead to more serious disorders and illnesses.

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